Hematuria Following Ingestion of Pyribenzamine Hydrochloride

Report of a Case

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WITH the widespread use of antihistaminic drugs, reports of toxic side-reactions have been increasing. Gastrointestinal and cerebral reactions predominate. In one of the most recent reports, Wolfson[3] noted urinary system disturbances following ingestion of pyribenzamine hydrochloride, with no gastric or cerebral reactions. In that case, the symptoms of diminishing urinary stream and increased bladder pressure, in the absence of any abnormalities in the urinary elements, indicated transient obstruction, probably in the region of the bladder neck.

A patient observed by the author had gross blood in the urine, associated with bladder pain, frequency and nocturia, after taking pyribenzamine hydrochloride.

CASE REPORT

A white male, aged 32, had been under observation and treatment for six months for chronic, non-specific prostatitis. Complete studies had indicated that there was no disease in the kidneys, as evidenced by normal intravenous pyelograms. In cystourethrograms taken several months before no abnormalities had been noted. In an effort to clear the prostatic infection, foci elsewhere were searched for. Chronic ethmoid sinusitis was present; and an otolaryngologist who, in consultation, diagnosed the condition as of allergic origin, treated the patient with sinus washings and then advised pyribenzamine hydrochloride in doses of 50 mg. four times a day. Two days after treatment with the antihistaminic agent was started, gross hematuria occurred. Associated with it were bladder pain, frequency of urination every 20 minutes during the day and hourly at night. The urine was grossly rust-colored, the reaction to a chemical test for blood was strongly positive, and innumerable erythrocytes per high-power field were noted in microscopic examination. Upon physical examination, no other toxic side-reactions were noted and no other condition that might cause the bleeding. The urethra and prostate were normal to palpation, as were the vesicles. Tenderness in the bladder was noted on deep palpation. The pyribenzamine was discontinued and urinary sedatives and antispasmodics were given. The following day, the bleeding was considerably diminished, but the urine still contained 50 to 60 erythrocytes per high-power field. There were no leukocytes. Reaction to a test for blood was 3+, and for albumin 2+. Within five days the symptoms had fully abated and the urine was microscopically normal.

DISCUSSION

The case reported is another in which urinary disturbances were noted following administration of pyribenzamine hydrochloride. In the previously reported case,[1] dysuria and increased frequency ceased in one day following discontinuance of the drug. In the present case, however, there was true hemorrhagic cystitis without actual infection. The mechanism was probably purely an irritative phenomenon. The author believes it likely that the excretion of the drug in the urine, in sensitive subjects, causes edema and exudation of the bladder mucosa, especially in the trigone region, much in the way that the formaldehyde of urotropin breakdown causes these conditions in the bladder of sensitive subjects. Wolfson[3] in his report indicated that "the antihistaminic may possess a spasmogenic property heretofore unrealized."

It would seem to be worth while for physicians giving pyribenzamine hydrochloride to question patients more frequently and more carefully with regard to urinary discomforts so that these complications may be avoided.

SUMMARY

The case reported is one in which gross blood appeared in the urine, with frequency, nocturia and bladder pain, following ingestion of pyribenzamine hydrochloride.

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Familial Occurrence of Polycythemia and Leukemia

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THE existence of polycythemia in two or more members of a single family has been reported by several observers, and in 1933 the cases previously reported in the literature were reviewed by Spodaro and Forkner,[15] who found six studies of what they believed to be proven familial polycythemia. These examples are cited briefly below.

Bernstein[2] described a polycythemic patient whose son had an erythrocyte count of 7.5 million and whose father, who died at the age of 47, had had a high color. In a family reported upon by Doll and Rothschild,[5] five members had Huntington's chorea; two of the five also had erythrocyte counts of six million or over, and one had hypertension. Another member also had hypertension, and the erythrocyte count was five million. Engelking[6] described polycythemic traits in three generations of a family; in the last generation, six of 13 children had erythrocyte counts ranging from 8 million to 13.6 million with hemoglobin value between 140 per cent and 185 per cent. In two the spleen was palpably enlarged, and in three there was clubbing of the fingers. Infantilism was coexistent with polycythemia in five of the children. Kretschmer[10] recorded polycythemia in three children in a single family. The father was not examined, but the mother was normal. In two of the three children, the clubbing of the fingers and toes and the cardiac findings led to suspicion that the polycythemia was secondary to congenital heart lesions. In the other instances, no such associated constitutional abnormalities were present. Tancré[16] reported a patient with an erythrocyte count of 14.2 million, hemoglobin value of 17.8 per cent and leukocyte count of 18,300. This patient had a sister with erythrocyte count of 6.1 million but no symptoms. Weil and Stieffel[18] described a patient with erythrocyte count ranging from 5.5 million to 7 million and hemoglobin values from 115 per cent to 130 per cent. Cyanosis of the lips and extremities was noted, and the liver and spleen were palpably enlarged. The patient's brother was cyanotic, and the erythrocyte count was 6.44 million. He had no symptoms, and the liver and spleen were not enlarged.

In addition to a review of the previously reported cases of familial polycythemia, Spodaro and Forkner[15] described a family in which splenomegaly as well as high erythrocyte

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counts (average 5.98 to 7.8 million) was observed in four members of the ten studied. Another member of the family had an enlarged spleen but normal erythrocyte count, and three other members had elevated erythrocyte counts (average of 5.92 to 6.91 million) but no enlargement of the spleen. The benign course of the disease, absence of leukocytosis, and the normal hemoglobin values and basal metabolic rates in all the patients in the family led Spodaro and Forkner to conclude that the condition differed from polycythemia vera, and they suggested the term "benign familial polycythemia."

In 1939, Nadler and Cohn[14] again reviewed the literature and in addition reported upon a family that they had studied in which four of 11 children had erythrocyte counts from 7.48 million to 8.8 million with hemoglobins from 21 gm. to 24.3 gm. per 100 cc. and packed red cell volume of 61 per cent to 69 per cent of the whole blood. The mother stated that these four children had had "red faces" since birth. There was no evidence of factors which might initiate secondary polycythemia. There was no hypertension, and in only one case was the spleen (barely) palpable. One child had Little's disease. All four children had abnormally high blood volume—from 95 cc. to 133 cc. per kilogram of body weight.

Thus, there seem to be eight authentic examples of familial polycythemia reported in the literature. Other investigators have described conditions which they thought were familial polycythemia, but insufficient evidence is given to establish the disease as familial, or the clinical and hematological data do not definitely point to this diagnosis.

Many instances of leukemia in two or more members of a single family have been reported, and the question of genetic factors has been discussed.[1, 4, 17] Videbaek[17] in 1947 reviewed the 26 reported instances of "apparently incontrovertible" familial leukemia, and added his own report of 13 families, making a total of 39 families in which the disease occurred in two or more members. Certainly it is rarely possible to find familial tendencies when study is made of a large number of patients with leukemia. In the authors' experience during the past 15 years with over 500 patients with leukemia, evidence of leukemia in immediate or distant relatives was found in only three or four families.

A review of the literature revealed four instances of both polycythemia and leukemia in a single family. Guggenheimer[7] reported the case of a patient with polycythemia whose mother died of leukemia. Gutzeit[8] reported a case in which a patient with polycythemia had a son who was treated for a "definite" lymphatic leukemia. In a case of polycythemia reported by Halse,[9] the patient's uncle died of leukemia. Videbaek[17] observed a patient with leukemia whose aunt was under treatment for polycythemia. In addition to the family reported in this presentation, the authors have under observation two other patients with polycythemia vera who have sisters who apparently died of leukemia. Otherwise, in a study of approximately 150 patients with polycythemia vera, there have been no other authentic examples of polycythemia or leukemia in close relatives.

In the family here reported upon, three of the members were referred for treatment of definite blood dyscrasia, and the mother had symptoms strongly suggestive of polycythemia. Other members of the family, unfortunately, were not available for study. Of the three patients studied, one had an established diagnosis of myelogenous leukemia which proved fatal three years later, and two had symptoms and physical and laboratory findings which were typical of polycythemia vera.

CASE REPORTS

CASE 1: A white housewife, aged 57, was well until September 1940, when she became aware of undue fatigue, slight loss of weight, and pain in the left leg at the site of rather large varicose veins. She entered a hospital for vein ligation, and in the course of a complete examination an abnormal blood picture typical of myelogenous leukemia was noted.

Prior to the onset of the symptoms described, the patient had been in excellent health. Five babies were delivered normally, and the children had no known blood abnormalities. In 1933, at the age of 50, menorrhagia developed, but after a uterine curettage a normal menstrual cycle was resumed until at age 52 menorrhagia developed again. Dilatation and curettage then were followed by complete cessation of menses, and the patient semed to be in good health until the onset of symptoms in 1940.

Family history. The mother died at the age of 78 of cardiovascular disease. During the last three years of her life she had had burning pain on the plantar surfaces of the toes with a bluish-red discoloration aggravated by exercise or heat and relieved by exposure to cold. The patient's father died at the age of 91 of causes incidental to age. There were 15 children in all. One brother, aged 67, now dead (see Case 2), had a known diagnosis of polycythemia, and a second brother had cardiovascular disease. A third brother had diabetes, an erythrocyte count of over 6 million, and hypertension which was treated by venesections. Five other brothers are living and well. One sister has known polycythemia. Five other sisters are living and well.

A report of the physical examination of the patient stated that she was observed to be well developed and nourished, appearing to be about the stated age. Slight pallor was noted but the skin was free of rashes. There were small tonsillar tags but no mucous membrane hemorrhages. The pupils reacted normally, and the optic fundi were considered normal. The thyroid gland was small, and the cervical nodes were not enlarged. The heart and lungs were normal to physical examination. The blood pressure was 130 mm. of mercury systolic and 70 mm. diastolic. On abdominal palpation an enlarged spleen could be felt extending 2½ inches below the costal margin on deep inspiration. Axillary and inguinal nodes were small. The extremities were normal except for varicose veins. Results of pelvic and rectal examinations were essentially normal, as were results of neurologic examination. Hematologic studies at the time of the initial examination showed the following: Erythrocytes numbered 4.31 million, with 2.6 per cent reticulocytes; and the hemoglobin content was 12.8 gm. per 100 cc. Leukocytes numbered 65,000 and platelets 2,517,000. The leukocyte differential was 2 per cent basophils, 35 per cent "C" myelocytes, 8 per cent "B" myelocytes, 2 per cent "A" myelocytes, 12 per cent metamyelocytes, 3 per cent band cells, 28 per cent segmented cells, 6 per cent lymphocytes, 4 per cent monocytes, 2 plus anisocytosis, and 1 plus poikilocytosis.

The patient was referred for treatment with radioactive phosphorus, and therapy was initiated in January 1941, at which time the leukocyte count was 130,700. After nine months of moderately intensive therapy, a remission was induced.[11] The patient then remained well clinically and in good hematologic remission until September 1942, when anorexia, nausea and vomiting developed, and subsequently fatigue, neuralgic pains in the legs, night sweats, and loss of weight. The leukocyte count began to rise gradually and immature forms were increasingly evident in spite of continued therapy. The condition of the patient deteriorated steadily, increasing anemia developed and the patient died January 5, 1943.

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CASE 2: A male physician, aged 68 when first observed by the authors, was in good health until 1927, when the patient was 54 years of age. At that time a painful burning sensation in the toes developed, accompanied by bluish-red dis-

colorations and slight swelling. Soon thereafter, the patient noticed hyperesthesia, tenderness, and discoloration of the fingers. These symptoms were decreased in the winter and were considerably aggravated in hot weather. A diagnosis of erythromelalgia was made,[3] and symptomatic relief was obtained with the use of acetylsalicylic acid. In 1934, the diagnosis of polycythemia was made, and therapy during the next four years consisted of phlebotomies at infrequent intervals without striking relief of symptoms. On one occasion pulmonary embolism occurred ten days after venesection. In 1939, phlebotomies were carried out to lower the erythrocyte count to a normal level, and the patient was placed on phenylhydrazine therapy which was continued for three years with slight relief of symptoms.

The patient had had pneumonia and empyema at age 6. Hypertensive vascular disease, pulmonary emphysema, and left renal calculus had been diagnosed before the patient was observed by the authors, and gout had been a complicating factor since 1930.

(The family history was described in Case 1.)

Upon physical examination the patient was observed to be pale and chronically ill. No lesions of the skin or mucous membranes were observed, and there was no lymph node enlargement. The cardiac outline was at the upper limit of normal size with a silhouette sugggestive of left ventricular hypertrophy. The blood pressure was 180 mm. of mercury systolic and 88 mm. diastolic. The heart rhythm was regular, and the rate normal. No murmurs were heard. The lungs were clear to auscultation. The spleen tip was palpable five finger-breadths below the costal margin on the left, and the liver edge extended four finger-breadths below the costal margin on the right. No cyanosis, edema, or clubbing were noted in the examination of the extremities. Hematologic studies revealed the following: Erythrocytes numbered 7.62 million, with hemoglobin 11.7 gm. per 100 cc.; leukocytes numbered 46,000, and platelets 450,000. The packed red cell volume was 40 per cent of the whole blood. The urine contained albumin (4+), four to seven erythrocytes per high-power field, numerous leukocytes, and occasional hyaline casts. The non-protein nitrogen content per 100 cc. was 50 mg., the uric acid content 10 mg. and the oxygen saturation 90 per cent.

Therapy with radioactive phosphorus[12] was begun in June 1942, and 20 millicuries was given over a period of two months. This was followed by definite subjective improvement with a disappearance of symptoms of both erythromelalgia and gout. The spleen decreased almost to normal in size and a progressive fall in the erythrocyte count from 7.62 million to 5.25 million was observed over a period of six months. During this time, the leukocyte count fell from 46,000 to 4,250. Additional P^{32} was given in 1943, 1944, and 1945, and a normal hematologic picture was maintained. During this time the subjective symptoms were minimal as long as the blood picture was kept within normal limits.

In 1945, nephrectomy was done on the left side because of abscess formation secondary to the kidney stone. Convalescence was uneventful, but elevation of the non-protein nitrogen level persisted. The course was gradually but progressively downhill until the patient died in uremia on June 22, 1947, at the age of 74. Necropsy was not done.

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CASE 3: The patient, a woman 54 years of age, first noticed dryness and intense itching of the skin in 1924 at the age of 38. In 1934 polycythemia was diagnosed and a correlation was noted between the severity of the pruritus and the number of erythrocytes in the blood. When the erythrocyte count was kept at the level of approximately 5 million by phlebotomies, the symptoms were ameliorated, although not relieved completely. X-ray therapy had never been used. More recently the patient had noticed small scattered purpuric spots over her body. Histamine injections, histaminase tablets, vitamin preparations, potassium chloride, and theelin in oil were tried at various times but did not relieve the symptoms. Previously the patient had been in good health. Thyroidectomy and tonsillectomy were uneventful, and three pregnancies were normal. The children are all well.

(The family history was described in Case 1.)

Upon physical examination, Feb. 11, 1941, rough, scaling, fissured skin lesions of eczematoid type, as well as scattered purpuric lesions, were noted. The tongue was serrated and reddened. The heart was enlarged slightly to the left. The blood pressure was 180 mm. of mercury systolic and 80 mm. diastolic. There was a blowing systolic murmur at the base of the heart. The abdominal musculature was relaxed; the spleen and liver could not be palpated.

Laboratory data, Feb. 11, 1941, were as follows: Erythrocytes numbered 5.01 million; the hemoglobin value was 76 per cent; leukocytes numbered 21,900. Therapy with phlebotomies was withheld and on Sept. 12, 1941, the erythrocyte count was 8.63 million, the hemoglobin value 111 per cent (15.3 gm. per 100 cc.), the platelet count 1,329,000, and the leukocyte count 27,900 with a normal cell differential.

Therapy with radioactive phosphorus[12] was begun with an initial dose of 6.9 millicuries Sept. 15, 1941. The blood cell counts gradually returned to normal and the hematologic remission continued until December 1943, when the cell counts were as follows: Erythrocytes 8.64 million with hemoglobin value of 118 per cent; leukocytes, 13,050. Packed cell volume was 62 per cent of the whole blood. During this time the pruritus had been greatly improved, although it was not completely eliminated. The patient was treated again with P^{32} in 1944 (6 millicuries in January and 7 millicuries in February), and complete hematologic remission was again induced. The itching lessened but was present to an annoying extent for several months before the blood cell counts rose again to polycythemic levels. On June 11, 1946, the results of blood examination were: Erythrocytes, 6.38 million; hemoglobin value 122 per cent (17.7 gm. per 100 cc.); leukocytes, 15,700; packed cell volume 55.8 per cent. At that time the spleen was palpable three finger-breadths below the left costal margin. Examination of sternal marrow revealed hyperplasia of the erythropoietic system with a Myeloid Erythroid ratio of 1.6:1. The oxygen saturation was 97 per cent. After several venesections, the blood cell counts on Oct. 25, 1946, were as follows: Erythrocytes, 7.8 million, with hemoglobin value 86 per cent; leukocytes, 18,550. Administration of 4 millicuries of P^{32} in December 1946 brought about a temporary drop in the blood cell counts, and additional P^{32} (3.2 millicuries) was given in July 1947, followed by a satisfactory remission and great improvement in clinical symptoms.

Comment: The case of myelogenous leukemia described in this instance presented no unusual features. The brother and sister were thought to have true polycythemia, and the absence of intense redness or cyanosis of the skin was attributed to the fact that each patient had been treated previously with phlebotomies and had small hypochromic red cells when first observed by the authors. In each case, the erythrocytosis was associated with leukocytosis and elevated platelet count. The hematocrit values were normal in each instance as a result of previous repeated bleedings, and the reticulocyte counts were never significantly elevated. The spleen was palpably enlarged in each case, but in one case (Case 2) the splenomegaly was a constant feature, whereas in Case 3 the spleen was palpable during active phases of the disease, but was not palpable when the disease was in hematologic remission.

It is unfortunate that all members of the family could not be studied even though they had no symptoms suggestive of blood dyscrasia. Only the mother had a history compatible with the diagnosis of polycythemia, and her symptoms of erythromelalgia were almost identical to those of the second patient in whom a definite relationship existed between these symptoms and the elevated erythrocyte count.

The cases reported herein differ considerably from those of so-called "benign familial polycythemia" described by Spodaro and Forkner[15] in regard to the severity of symptoms necessitating intensive therapy, as well as the presence of other features commonly seen in association with polycythemia vera, namely, the leukocytosis, the high platelet count, and in one instance, gout and erythromelalgia.[3] The occurrence of two cases of polycythemia vera and one case of leukemia in a single family is of particular interest in the light of the high incidence of leukemia occurring as a complication of polycythemia rubra vera[12, 13] and because so few reports of the occurrence of both polycythemia and leukemia in a single family were found in the literature.

SUMMARY

There are eight authentic examples of familial polycythemia and 39 instances of familial leukemia reported in the literature, but the authors found only four instances of the occurrence of both polycythemia and leukemia in the members of one family.

In the family studied by the authors, two cases of polycythemia and one case of myelogenous leukemia in a brother and two sisters are reported. The possible existence of polycythemia in an earlier generation of the family could only be conjectured.

The two patients diagnosed as having polycythemia had typical features of polycythemia vera and responded well to radioactive phosphorus therapy.

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